UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 10/563,399 | 01/05/2006 | Alan Berry | 21841USWO(C038435/0196234 | 3243 |

7590 02/01/2008

Stephen M Haracz
Bryan Cave
1290 Avenue of the Americas
New York, NY 10104

| EXAMINER | |
|---|---|
| RAGHU, GANAPATHIRAM | |
| **ART UNIT** | **PAPER NUMBER** |
| 1652 | |

| MAIL DATE | DELIVERY MODE |
|---|---|
| 02/01/2008 | PAPER |

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/563,399 | BERRY ET AL. | |
| | Examiner | Art Unit | |
| | Ganapathirama Raghu | 1652 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *10 December 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-7* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

### *Application Status*

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 12/10/07 has been entered.

In response to the Final Office Action dated 06/04/2007 and an Advisory Action dated 10/25/07, applicants' filed an RCE received on 12/10/07 is acknowledged. The RCE contains the same set of claims as presented on 10/09/07. Claims 1-7 are pending and are under consideration in the instant Office Action.

Objections and rejections not reiterated from previous action are hereby withdrawn.

### *Maintained--Claim Rejections: 35 USC § 103*

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:
> 1. Determining the scope and contents of the prior art.
> 2. Ascertaining the differences between the prior art and the claims at issue.
> 3. Resolving the level of ordinary skill in the pertinent art.
> 4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various

claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-7 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gokarn et al., (WO 02/26933 A2, publication date 04/04/2002, in IDS), in view of Yoshida et al., (J. Gen. Appl. Microbiol., 1998, Vol. 44: 19-26; in IDS) and Berry et al., (WO 02/099095 A2, publication date 12/121/2002; in IDS). Claims 1-7 are directed to a process for CoQ10 production, comprising introducing a mevalonate operon of a microorganism belonging to the genus *Paracoccus* into a microorganism belonging to the genus *Rhodobacter* and said modified microorganism. Gokarn et al., (*supra*) disclose the identification of polynucleotide sequences involved in the isoprenoid production and also use of *Rhodobacter sp.*, microorganism for the production of CoQ10 by introducing heterologous genes involved in the isoprenoid production (CoQ10), including transformation procedures in said microorganism (lines 13-29, page 8; lines 10-34, page 9; pages 45-51; Examples 5, 8 and 14; Fig.1). Gokarn et al., is silent regarding production of CoQ10 in *Rhodobacter sp.,* by transforming said microorganism with a plasmid pBR-K-mev-op-R114 comprising a mevalonate operon of a microorganism of *Paracoccus zeaxanthinifaciens.* Yoshida et al., (*supra*) disclose that *Rhodobacter sphaeroides* as an excellent producer and host for the production of ubiquinone-10 (CoQ10), an isoprenoid compound (Abstract and Introduction section, page 19). Both Gokarn et al., and Yoshida et al., further lend support that *Rhodobacter sphaeroides* would be an excellent host cell with necessary metabolic

machinery for the synthesis of CoQ10 by heterologous expression of polynucleotides involved in the mevalonate pathway and encoding polypeptides. Berry et al., et al., (*supra*) disclose the sequence of plasmid pBR-K-mev-op-R114, comprising a mevalonate operon of *Paracoccus zeaxanthinifaciens* strain ATCC 21588, wherein said mevalonate operon comprises polynucleotides that encode MvaA (hydroxymethyglutaryl-CoA reductase), Idi (isoprenyl diphosphate isomerase), Hcs (hydroxymethyglutaryl-CoA synthase) Mvk (mevalonate kinase), Pmk (phosphomevalonate kinase) and Mvd (diphosphomevalonate decarboxylase), the source of the genomic DNA of the instant application and the methods for plasmid construction and use of the same for transforming microorganism of interest. Therefore, it would have been obvious to a person of ordinary skill in the art to combine the teachings of Gokarn et al., Yoshida et al., and Berry et al., to generate a recombinant *Rhodobacter sphaeroides* comprising a mevalonate operon of *Paracoccus zeaxanthinifaciens* as such a recombinant would produce enhanced levels of CoQ10. Motivation to generate such a modified microorganism derives from the fact that CoQ10 is a commercial product of importance in health, nutrition and pharmaceutical industry. The expectation of success is high, because Gokarn et al., and Yoshida et al., teach that *Rhodobacter* by virtue of its endogenous cellular machinery and amenable to transformation with mevalonate biosynthetic pathway genes would certainly be a good host cell for enhanced production of CoQ10. Berry et al., teach yet another pathway, use of a mevalonate operon of *Paracoccus* that could be used to transform *Rhodobacter* for enhanced production of CoQ10. Therefore, Claims 1-7 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gokarn et al., (WO 02/26933 A2, publication date 04/04/2002, in IDS)), in view of Yoshida et al., (J. Gen.

Appl. Microbiol., 1998, Vol. 44: 19-26; In IDS) and Berry et al., (WO 02/099095 A2, publication date 12/121/2002; in IDS).

Applicants have traversed this rejection with the following arguments:

(A) The combined references do not teach or suggest the objective of the instant invention.

(B) "all claim limitations must be taught or suggested by the prior art".

(C) "the rejection is devoid of any evidence- or even argument in support of the proposed combination".

(D) "Berry's other disclosure is against well established precedent. A prior art reference must be considered in its entirety", and "Yoshida et al., is at best non-analogous art and cannot be cited and at worst is irrelevant to the present claims".

Reply: (A) & (B): Applicant's arguments are directed against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

The cited references are in "congruence" with obviousness rejection and teach all limitations of the instant claims i. e., meet all the criteria and parameters (Teaching, Suggestion and Motivation) as defined by *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966) and the rationale for TSM test (Teaching, Suggestion and Motivation) according to KSR ruling.

Examiner is reproducing the section of the disclosure by Gokarn et al., to support the argument that the knowledge of biosynthetic pathways in the synthesis of carotenoids, isoprenoids including CoQ10 (Gokarn et al.,), host cells i.e., *Rhodobacter*, inherently having the

ability to synthesize CoQ10 (Gokarn et al., and Yoshida et al.,) and structural elements encoding the mevalonate-dependent pathway (Berry et al.,) were well known in the art.

**1) Gokarn et al.,**

ISOPRENOID PRODUCTION
BACKGROUND

1. Technical Field
The invention relates to methods and materials involved in the production of isoprenoids.

2. Background lnformation
Isoprenoids are compounds that have at least one five-carbon isoprenoid unit. Examples of isoprenoid compotmds include, without limitation, carotenoids, isoprenes, sterols, terpenes, and ubiquinones. Various enzymatic pathways in plants, animals, and microorganisms result in the synthesis of isoprenoid compounds. Typically, isopentenyl diphosphate (IPP), dimethylallyl diphosphate (DMAPP), or combinations thereof are polymerized to form isoprenoid compounds.

Two pathways can be used to produce IPP. The first pathway, known as the mevalonate-dependent pathway, produces IPP from 3-hydroxymethyl-3-methylglutaryl Coenzyrne A (HMGCoA) in a series of reactions. The second pathway, known as the mevalonate-independent pathway, produces IPP from 1-deoxyxylulose-5-phosphate (DXP) in a series of reactions. One of those reactions involves the use of DXP synthase (DXS) to catalyze the condensation ofpymvate and glyceraldehyde-3-phosphate to form
DXP.

Once made, IPP can be used to make various isoprenoid compounds. Specifically, enzymes known as polyprenyl diphosphate synthases catalyze polymerization reactions that combine IPP and DMAPP to form compounds known as polyprenyl diphosphates. For example, decaprenyl diphosphate synthase (DDS) catalyzes the consecutive condensation of IPP with allylic diphosphates to produce decaprenyl diphosphate. Decaprenyl diphosphate is a polyprenyl diphosphate that can be used to form the side chain of a ubiquinone known as CoQ(10). Other polyprenyl diphosphate synthases include, without limitation, farnesyl-, geranyl-, and octapreneyl diphosphate synthases.

**2)** Furthermore, **Gokarn et al., and Yoshida et al.,** provide the motivation to introduce mevalonate biosynthetic pathway genes into *Rhodobacter* by virtue of the teachings that a) *Rhodobacter* has endogenous cellular machinery to synthesize CoQ10 and b) amenable to transformation, would certainly be a good host cell for enhanced production of CoQ10.

**3)** The reference of **Berry et al.,** (*supra*) disclose the structural element of the instant invention i.e., sequence of plasmid pBR-K-mev-op-R114 comprising a mevalonate operon of a microorganism of *Paracoccus zeaxanthinifaciens*.

Reply: (C) & (D): Examiner continues to hold the position that the cited references render claims 1-7 *prima facie* obvious to one of ordinary skill in the art when one applies the Teaching, Suggestion and Motivation (TSM) test under the rationale for arriving at a conclusion of obviousness as suggested by KSR ruling. See the recent Board decision Ex parte Smith, -- USPQ2d--, slip op. at 20 (Bd. Pat. App. & Interf. June 25, 2007)(citing KSR, 82 USPQ2d at 1396). The rationale applied for the rejection and maintaining the rejection are as follows:

(1) Combining prior art elements according to known method to yield predictable results.

(2) Simple substitution of one known element for another to obtain predictable results.

(3) "Obvious to try"- choosing from a finite number of identified, predictable solution, with a reasonable expectation of success.

All the elements including Teaching, Suggestion and Motivation are provided in the cited prior art as Gokarn et al., and Yoshida et al., provide the motivation to use of *Rhodobacter* for the reasons cited above and Berry et al., teach the isolation of pBR-K-mev-op-R114 comprising a mevalonate operon of a microorganism of *Paracoccus zeaxanthinifaciens* comprising the structural elements of the instant invention for the production CoQ10 as per the factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a).

Therefore, combining the teachings of the above references it would have been obvious to one of ordinary skill in the art at the time of the instant invention to generate a bacterium that

can be used for a process in the production CoQ10 and such a bacterium and said process would comprise introducing a mevalonate operon of a microorganism belonging to the genus *Paracoccus* into a microorganism belonging to the genus *Rhodobacter*.

The cited references teach every single element of the instant invention such as, 1) Gokarn et al., and Yoshida et al., teach that *Rhodobacter* by virtue of its endogenous cellular machinery inherently posses the increased ability to synthesize CoQ10 and amenable to transformation with mevalonate biosynthetic pathway genes and therefore, would certainly be a good host cell for enhanced production of CoQ10; 2) The reference of Berry et al., (*supra*) disclose the structural element of the instant invention, sequence of plasmid pBR-K-mev-op-R114 comprising a mevalonate operon of a microorganism of *Paracoccus zeaxanthinifaciens*. Therefore a skilled artisan would certainly select *Rhodobacter* as the first choice organism for the production of CoQ10 and examiner has clearly and lucidly expressed this "obvious" point why a skilled artisan would choose *Rhodobacter* as the preferred cellular context as it provides all the additional advantages possibly other enzymes, cofactors and substrates for efficient production of CoQ10 and therefore under such a cellular context one would achieve optimal expression of plasmid pBR-K-mev-op-R114 comprising a mevalonate operon encoding polypeptides for the optimal production of CoQ10.

Moreover, the objectives of the cited references need not be the same as the instant invention to be used in an "Obviousness" rejection, the only requirement is the findings of cited prior art need to either Teach or provide Motivation or Suggestion or Elements that when combined by a skilled artisan would render the instant invention "Obvious". The cited references are also certainly directed to the production of CoQ10, wherein the studies were designed to

identify and enhance the production of CoQ10 and therefore are analogous art and the elements taught in the cited prior art when combined would yield high expectation of success. The instant invention is simple substitution and extension of findings of Gokarn et al., Yoshida et al., and Berry et al., wherein the elements of prior art are combined to yield predictable results and the choice is from a finite number of identified elements in prior art with highly predicatble outcome and expectation of success. Finally the KSR ruling forecloses the argument that a specific Teaching, Suggestion or Motivation is more than enough for obviousness to try and thus provides support for finding of "Obviousness" (Ex parte Smith, --USPQ2d--, slip op. at 20, Bd.Pat. Appl. & Interfer. June 25, 2007, citing KSR USPQ2d at 1396).

***Summary of Pending Issues***

The following is a summary of issues pending in the instant application.

Claims 1-7 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gokarn et al., (WO 02/26933 A2, publication date 04/04/2002, in IDS), in view of Yoshida et al., (J. Gen. Appl. Microbiol., 1998, Vol. 44: 19-26; in IDS) and Berry et al., (WO 02/099095 A2, publication date 12/121/2002; in IDS).

***Allowable Subject Matter/Conclusion***

None of the claims are allowable.

Applicants must respond to the rejections in each of the sections in this Office Action to be fully responsive for prosecution.

Claims 1-7 are drawn to the same invention claimed in the application prior to the entry of the submission under 37 CFR 1.114 and could have been finally rejected on the grounds and

art of record in the next Office action if they had been entered in the application prior to entry under 37 CFR 1.114. Accordingly, **THIS ACTION IS MADE FINAL** even though it is a first action after the filing of a request for continued examination and the submission under 37 CFR 1.114. See MPEP § 706.07(b). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

***Final Comments***

To insure that each document is properly filed in the electronic file wrapper, it is requested that each of amendments to the specification, amendments to the claims, Applicants' remarks, requests for extension of time, and any other distinct papers be submitted on separate pages.

It is also requested that Applicants identify support, within the original application, for any amendments to the claims and specification.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ganapathirama Raghu whose telephone number is 571-272-4533. The examiner can normally be reached on M-F; 8:00-4:30 pm EST. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapu Achutamurthy can be reached on 571-272-0928. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300 for regular communications and for After Final

communications. Any inquiry of a general nature or relating to the status of the application or proceeding should be directed to the receptionist whose telephone number is 571-272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Ganapathirama Raghu, Ph.D.

Patent Examiner
Art Unit 1652
Jan. 19, 2008.

TEKCHAND SAIDHA
PRIMARY EXAMINER